CD93 Marks a Non-Quiescent Human Leukemia Stem Cell Population and Is Required for Development of MLL-Rearranged Acute Myeloid Leukemia.

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Authors: Masayuki Iwasaki, Michaela Liedtke, Andrew J Gentles, Michael L Cleary

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Public Summary:
A general consensus is that leukemia stem cells share with hematopoietic stem cells the crucial property of cell cycle quiescence, along with self-renewal capability and expression of similar immunophenotypes. These shared features complicate efforts to eradicate acute leukemia by therapeutically targeting leukemia stem cells without adversely affecting hematopoietic stem cells. This study demonstrates that the vast majority of leukemia stem cells in a distinctive genetic subtype of AML are actually non-quiescent cells. Although human leukemia stem cells are enriched in the a phenotypic compartment that is generally highly quiescent, expression of the lectin CD93 further separates out leukemia stem cells, which prove to be actively cycling, non-quiescent AML cells. Furthermore, CD93 is required for leukemogenesis and the underlying mechanism is predominantly due to silencing of a major tumor suppressor in AML, to regulate leukemia stem cell self-renewal.

Scientific Abstract:
Leukemia stem cells (LSCs) are thought to share several properties with hematopoietic stem cells (HSCs), including cell-cycle quiescence and a capacity for self-renewal. These features are hypothesized to underlie leukemic initiation, progression, and relapse, and they also complicate efforts to eradicate leukemia through therapeutic targeting of LSCs without adverse effects on HSCs. Here, we show that acute myeloid leukemias (AMLs) with genomic rearrangements of the MLL gene contain a non-quiescent LSC population. Although human CD34(+)CD38(-) LSCs are generally highly quiescent, the C-type lectin CD93 is expressed on a subset of actively cycling, non-quiescent AML cells enriched for LSC activity. CD93 expression is functionally required for engraftment of primary human AML LSCs and leukemogenesis, and it regulates LSC self-renewal predominantly by silencing CDKN2B, a major tumor suppressor in AML. Thus, CD93 expression identifies a predominantly cycling, non-quiescent leukemia-initiating cell population in MLL-rearranged AML, providing opportunities for selective targeting and eradication of LSCs.